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—Editorial—

Case Finding Among Private Patients

It is recognized that there are many reasons for the rapid decline in the incidence of tuberculosis during the past 50 years. It is impossible to evaluate accurately, or even approximately, the relative influence of complex socioeconomic conditions and of control measures in bringing about this favorable result.

In 1937, Wade H. Frost concluded that the point had been reached in the United States where there is a gradual downward trend in the incidence of tuberculosis, and that, barring major upsets in civilization, the eventual eradication of the disease can be expected. The continued decline in the annual number of deaths from tuberculosis during the past 12 years, in spite of the adverse conditions caused by a great war, is ground for confidence in the accuracy of Frost's conclusion.

Even though control measures are only one factor in the eradication of tuberculosis, they may very well be the *decisive* factor. Anything which will reduce the size of the reservoir of the tubercle bacillus in human beings will lessen the number of new cases of tuberculosis. Every case of the disease, actually or potentially infectious, which is discovered and brought under control is a step in reducing the size of this reservoir. In the aggregate, control measures may represent the weight which will tip the balance in favor of the human race. It is this consideration which gives importance to any method which discloses a considerable number of cases of tuberculosis, and especially of those which are symptomless.

Although statements to the contrary have been made recently, nothing is more completely proved than the fact that approximately one-half of all cases of significant tuberculosis have no symptoms, or symptoms so slight as to escape notice. According to the National Tuberculosis Association estimates, there are a quarter of a million unknown cases of tuberculosis in the United States—at least as many

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as there are known cases—and recent experience indicates that the unknown cases far outnumber the known. In the 1948 mass survey in Washington, D. C., 4,098 out of 4,665 cases of tuberculosis discovered were previously unknown to the health department. Similar findings have been reported in all other large surveys.

From its small beginnings during the decade 1930-40, the mass survey method for tuberculosis detection has advanced in the United States to the point where at present about 14 million people annually undergo chest X-ray examinations. This is a significant achievement, and although it can be extended until the equipment already existing is fully utilized, it still does not represent a case-finding rate sufficiently high to insure control of the disease in any reasonable time. It is important that the mass survey programs be enlarged, but, in the meantime, every method which promises disclosure of a considerable number of cases of tuberculosis should be utilized.

Sixty to eighty million Americans, for one reason or another, annually consult a doctor, and it is known that the tuberculosis rate among them is much higher than among the general population. For this reason it is highly desirable that private physicians, including general practitioners, internists, and specialists, obtain a survey film of every patient who consults them unless the results of a recent chest X-ray survey are available.

It has been the practice of some radiologists for many years to make a single film of the chest in cases referred for other examinations, especially in cases referred for gastrointestinal study. This has disclosed many unsuspected chest conditions including tuberculosis. Now that photofluorography has greatly reduced the cost of such a survey film, it should become routine practice among radiologists; its quite nominal cost can be absorbed in the major examination.

This reservoir of cases, however, is small compared with the vast number who consult general practitioners and internists. Methods can undoubtedly be devised whereby all such patients, at least those who are 15 years of age or older, can have a survey film made without cost to the patient—even a small charge would probably prevent wide use of the method.

It is not necessary that any one method be adopted to accomplish the desired end. In some communities, the local or State health department could, perhaps, defray the cost as part of the general tuberculosis prevention program, especially in view of the fact that case finding in the smaller group would be relatively much more productive than in the usual mass survey. In other communities, it could be done by the tuberculosis association. In still others, general hospitals which have adopted a hospital admission X-ray survey program could enlarge the program to include survey films for the private patients of members of the hospital staff. Furthermore, it

could very well become general practice among radiologists to make available such service to the general profession.

The details of such a program may seem numerous and difficult at first thought, but they can be worked out. The first essential for its success is the interest of the private physicians of each community. They are in the best position to promote it and to carry it out.

Today, because of procedures which have become routine, the private physician's office is a bulwark against such diseases as smallpox and diphtheria. In like manner, it can become one of the most effective agencies for tuberculosis control. By promoting such a public health measure, the general practitioners of the Nation would be acting in line with the great tradition of the profession as a force for prevention as well as cure of disease.

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Tuberculosis Case Finding in General Hospitals

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For many years, the chest X-ray has been recognized as a superior method of diagnosing pulmonary tuberculosis, but when only large films could be used, the cost in time and facilities prevented its general use to screen out tuberculosis among large groups of people. The fluoroscope was tried in some hospitals, and in the hands of expert clinicians it was recognized as a valuable diagnostic aid, but it failed to supply an objective record of the findings. The development of the small film photofluorograph in the late 1930's made possible the examination of large numbers of people quickly, easily, and at a relatively low cost, and gave impetus to tuberculosis case-finding programs which have expanded greatly in the past 10 years. Limited progress has been made, however, in the development of case-finding programs in general hospitals.

The responsibility of the general hospital in tuberculosis control is not a new concept. The American Hospital Association has been on record since 1921 as urging provisions for at least temporary care of tuberculous patients in general hospitals. Even before the development of small-film photofluorography, programs for routine chest X-ray of all admissions were recommended at Association meetings. In 1942, a pamphlet issued by the Association included specific suggestions for such programs. Similar recommendations have been made by the American Medical Association, the United States Public Health Service, the National Tuberculosis Association, the American Trudeau Society, and other State and national organizations and agencies.

Early interest in tuberculosis case finding in general hospitals was aroused as a result of programs in hospitals where tuberculin tests and chest X-rays were made on medical and nursing students. It was found that a large number of students who had entered as nonreactors had become positive tuberculin reactors shortly after beginning to work with patients, even in hospitals which did not knowingly admit tuberculous patients.

In 1943, the Committee on Hospital Personnel of the American Trudeau Society and the American Hospital Association sent questionnaires to 934 hospitals with schools of nursing to determine practices regarding tuberculosis. The results obtained from this survey indicated that 85 percent made X-rays of their student nurses; 28

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percent, of medical students; 31 percent, of graduate nurses; and 17 percent, of other employees. The Committee reported that in spite of wartime difficulties, 56 hospitals took X-rays of all admitted patients (1).

Studies of the Problem

Evidence of unrecognized cases of tuberculosis in general hospitals, and the results obtained from routine X-ray examinations of persons admitted to general hospitals and clinics were reported in the studies reviewed below. Information is included concerning the development of programs, the objectives and principles which are involved, and procedures which have proved effective.

Since this paper is concerned with tuberculosis case finding, other chest lesions discovered through routine X-ray of patients admitted to general hospitals will not be discussed. Similarly, tuberculosis among hospital personnel will be considered only in relation to the historical development of the program.

Swedish Hospital, Minneapolis, Minn.

Mills and Stewart (2) conducted a survey at Swedish Hospital, Minneapolis, Minn., during the month of January 1932, in which 586 persons including patients, employees, and graduate and student nurses were given Mantoux tests followed by X-ray examination of all positive tuberculin reactors. Diagnosed cases of advanced tuberculosis admitted to the hospital during the month were not included in the survey. A total of 353 patients were tested, of whom 67 were positive reactors to tuberculin. Of these, 47 had X-ray examinations, and evidence of tuberculosis reinfection was found in 7.5 percent of the cases X-rayed. Five persons who were admitted to the hospital for other conditions were proven to have reinfection type tuberculosis; all five were free from symptoms suggesting tuberculosis. A chest X-ray might have been recommended for one person who had asthma.

University Hospital, Ann Arbor, Mich.

Hodges, (3, 4, 5) of University Hospital, Ann Arbor, Mich., made one of the early studies of routine X-rays of hospital admissions which led to the conclusion that unrecognized cases of tuberculosis could be found through preliminary chest X-ray of all hospital admissions.

The study was made during 11 working days from June 27 to July 13, 1935; a total of 1,116 patients were X-rayed, and 1,101 satisfactory films were taken. Of this number, 8.1 percent showed evidence of lung changes, and approximately 1 percent of the patients were found to have significant chest conditions suggestive of active tuberculosis.

Criteria were set up prior to the study to determine whether it would be profitable to make a chest X-ray on all persons registering at the University Hospital. It was decided on the basis of the findings that through this method (1) greater diagnostic accuracy is possible (14 persons in this group with no symptoms indicating the need of X-ray were found to have questionable lesions); (2) the speed of diagnosis is increased; (3) the cost is not prohibitive and could be borne by the hospital with no extra charge to the patient; and (4) the X-ray department is strengthened in the long run, since more cases are referred for additional X-ray than would otherwise be requested. This study is frequently quoted in the literature since accurate records were kept, and it was conducted to test a specific hypothesis.

In April 1939, the Kellogg Foundation gave the money for building alterations and equipment necessary for X-rays to be made on all patients admitted to the University Hospital. This program began operations on July 1, 1941, and during the first 4 weeks, 7,841 persons were examined. Of these, 9.3 percent showed evidence of abnormal chest conditions which needed further study; 0.8 percent had tuberculosis in active form. The experience in this hospital will be discussed later in relation to methods which may be applicable to programs in other general hospitals.

Survey in Up-State New York

To determine the size of the tuberculosis problem in general hospitals, Plunkett and Mikol (6, 7) made a study of 4,853 adult admissions to 14 hospitals in 10 cities of up-State New York in 1937-38. Interest in making the study was stimulated by the fact that about 10 percent of the total deaths from tuberculosis in the area during 1936-37 occurred in hospitals with no provision for care of tuberculosis patients; 74 percent of these deaths were due to pulmonary tuberculosis, and 61 percent were not reported as such until after death.

The hospitals included in the study were selected at random and diversified as to bed patients; 4 were in cities under 50,000; 3, in cities between 50,000 and 100,000; and 7, in cities over 100,000 population. Patients over 15 were selected for X-ray excluding acutely ill patients, known cases of tuberculosis, and persons admitted to the tuberculosis service and out-patient departments. Films which showed significant or questionable lesions were read by personnel in the division of tuberculosis, State department of health, and returned to the hospital with the report of findings.

The incidence of reinfection tuberculosis and clinically significant disease discovered in these 14 hospitals through routine chest X-ray examinations of hospital admissions in 1937-38 was as follows:

<i>Films studied</i>	<i>Evidence of reinfection</i>		<i>Clinically significant lesions</i>	
	<i>Number</i>	<i>Percent</i>	<i>Number</i>	<i>Percent</i>
4, 853	128	2. 6	51	1. 1

In 27 of the cases with clinically significant lesions (or 0.6 percent of the total number), tuberculosis had not been considered a possibility, and the disease would probably have been overlooked had not the X-ray been a routine procedure. Five of these cases were diagnosed as far advanced, 12, as moderately advanced, and 10, as in the minimal stage of the disease. There was no significant difference in the proportion of cases found in the various departments—medical, surgical, and obstetrical. None of the cases found had been previously reported.

The authors applied the 0.6 percent yield of unsuspected clinically significant tuberculosis found in this study to the number of adult admissions in general hospitals throughout the United States for 1947 and estimated that, provided similar conditions prevailed in the other hospitals of the country, more than 40,000 unrecognized cases of pulmonary tuberculosis are admitted to general hospitals each year.

It was pointed out in this study that general hospital admissions constitute a special population group which is readily accessible for study and handling under ideal conditions since professional personnel and scientific equipment are easily available for the necessary diagnostic services. It was noted that X-ray may be looked upon as costly, but that human economy should be considered as important if not more important than administrative economy.

The benefits to the hospital in initiating the program were listed as: (1) protection of personnel, (2) provisions for a permanent record of the patient, (3) improvement in staff efficiency, and (4) better service to patients. The suggested benefits to the community were: (1) more effective case finding, (2) earlier diagnosis of cases when treatment is more effective, (3) greater protection through the isolation of open cases, and (4) the discovery of other significant chest conditions.

Meyer Memorial Hospital, Buffalo, N. Y.

In 1939–42, Farber and Clark (8) made a study in Meyer Memorial Hospital, Buffalo, N. Y., to evaluate the danger imposed upon hospital personnel by unrecognized cases of tuberculosis. Although all known cases of tuberculosis in the hospital were isolated on wards of the tuberculosis service, and all suspects were isolated on special wards where contagious disease techniques were employed, previous records showed that approximately 30 to 35 percent of the students became tuberculin reactors in their first year before assignments to either of these wards. This suggested that unsuspected tuberculosis on general wards was an important source of tuberculosis infection in students.

In order to test this hypothesis, an analysis was made of the records of 100 patients admitted to the hospital during 1937-38 with other diagnoses and later found to have significant tuberculosis. Clinical information on each of these patients was then correlated with his location in the hospital and the number of days before diagnosis was established. The authors believed that many other cases of tuberculosis which had never been diagnosed were in the hospital at this time. Approximately 30,000 patients were admitted to the hospital during this period, and the 100 cases which were studied would represent only about one-fourth of the number of tuberculosis patients that would have been expected on the basis of Plunkett's study, which has already been discussed.

The records of the 100 patients were studied to determine the length of time hospital personnel were exposed to the disease before diagnosis was established. It was found that a total of 1,497 hospital days had been spent on the various hospital wards before transfer to the tuberculosis ward; the actual number of days before transfer ranged from 1 to 146 days with a median of 8 days. Eighty-one percent of these patients had advanced tuberculosis at time of diagnosis and 60 percent had positive sputum. Seventy-nine percent were men with a median age of 54; 21 percent were women with a median age of 33.

The authors concluded from these findings that every patient with sputum should have examinations for tuberculosis, including X-ray and laboratory study. The conclusions were also reached that (1) if all adult patients admitted to the general hospital were X-rayed, much tuberculosis would be discovered, and (2) unrecognized cases of tuberculosis create a significant public health problem since they constitute a hazard to hospital personnel and other patients.

In 1947, Scatchard and Duszynski (9) reported on the program which was begun in 1944 in Meyer Memorial Hospital as a result of Farber and Clark's work.

Ten thousand examinations were made between July 8, 1944 and November 12, 1945. The uncorrected figure for previously unsuspected tuberculosis was found to be 3.7 percent, and 1.8 percent were proven to have the disease by sputum examination or autopsy. In one group of 3,000 examinations, 63 cases of tuberculosis were discovered. A review of 49 of these cases revealed that 5 did not have active tuberculosis, 9 had positive sputum, 8 had proven tuberculosis on necropsy; 5 were transferred at once to the tuberculosis division and proven there; the remaining 22 were inadequately studied. The authors stated in their summary that in their opinion at least 2.5 percent of the new patients studied had pulmonary tuberculosis, and that, in addition, a large number of patients had other lesions which needed further study and care.

Grasslands Hospital, Valhalla, N. Y.

Childress, Debbie, and Harmon (10) reported on a demonstration at the Grasslands Hospital, Valhalla, N. Y., extending over a period of 18 months from July 1, 1941, to January 1, 1943. This program was financed by the Grasslands Hospital, the Westchester Tuberculosis Association, and the Westchester County Department of Health. The purpose of the program was to study and demonstrate the yield of tuberculosis cases which would be expected by routine chest X-ray or fluoroscopic examination of patients admitted to the hospital and to the outpatient department, who were not suspected of having pulmonary disease and would not be customarily examined by X-ray. Persons under treatment for pulmonary and cardiac disease who would have received such an examination were omitted from the study.

Clinic patients were examined by fluoroscope, and X-rays were made if it was considered necessary; 14- by 17-inch X-rays were made of hospital patients. Fluoroscopies were done by physicians in the tuberculosis and X-ray departments, and the films were interpreted by the roentgenologist and physician in charge. Most of the cases were studied by the physician on the tuberculosis service.

Table 1. *Tuberculosis in general hospital patients, Grasslands Hospital, Valhalla, N. Y., July 1, 1941-Jan. 1, 1943, as revealed by X-ray examination of hospital admissions*

Patients	Number	Percent
Admitted to hospital.....	9,693	100
Examined.....	7,187	74
Showing tuberculosis by X-ray.....	290	4
Showing evidence of reinfection disease.....	201	2.8

Evidence of manifest tuberculosis was present in 290, or 4 percent of the cases, and 201, or 2.8 percent, showed evidence of reinfection disease. Of the total, 42, or 0.6 percent, were classified as active or questionably active; 3, active primaries.

This program was considered an extension of one already in operation for employees and medical and nursing student. The authors concluded (1) that although tuberculosis case-finding programs among various sections of the population have increased the opportunity for finding tuberculosis, the general hospital X-ray equipment has not been fully utilized, and (2) that by discovering previously unrecognized tuberculosis among the patients, better protection is offered the hospital worker through the isolation and treatment of infectious cases.

Flushing Hospital, Flushing, N. Y.

Epstein and Meliss (11) reported on a program conducted in Flushing Hospital, Flushing, N. Y., August 1944-July 1945, in cooperation with the Queensboro Tuberculosis and Health Association. A total

of 3,487 persons were X-rayed: 112, or 3.2 percent, had reinfection type tuberculosis; 21, or 0.6 percent, showed evidence of active disease; and 13, or 0.37 percent, were not suspected before being X-rayed.

University of Chicago Clinics, Chicago, Ill.

Bloch and Tucker (12) reported on the experience in the University of Chicago clinics where routine fluoroscopy of the chest of all patients, regardless of the nature of their complaints, has been an accepted procedure since 1942. The first 15,000 examinations produced a total of 626 persons, or 4.17 percent, who were found to have tuberculous lesions of the reinfection type; 1.43 percent had lesions which were considered clinically important. The findings in the various clinics, classified as to clinical importance, are given in the following table.

Table 2. Tuberculosis by clinical importance, found on routine fluoroscopy of 15,000 patients at the University of Chicago clinics. 1942-44

	460 cases in chest clinics	14,540 cases in other clinics
Clinically important.....	Percent 17.8	Percent 0.9
Clinically unimportant.....	13.0	2.4
Total tuberculosis.....	30.8	3.3

The findings in the University of Chicago clinics were compared with those of a previous study made by Bloch, et al. (13) in Chicago of 25,000 Negroes who were examined at Provident Hospital where, since 1939, chest fluoroscopy has been provided for all clinic patients regardless of their complaints. In this group tuberculosis other than primary infection was found in 4 percent of the total number examined, and 2.6 percent had a clinically important disease. The findings in the two groups are compared in table 3.

The authors estimated from this experience that in the United States 600,000 persons with active pulmonary tuberculosis come under medical treatment each year for some other complaint without the lung involvement being recognized.

Table 3. Tuberculosis by clinical importance found by fluoroscopy, in University of Chicago clinics 1942-44, and in Provident Hospital clinics 1939-44, Chicago, Ill.

	15,000 cases, University of Chicago clinics		25,000 cases, Provident Hospital clinics	
	Number	Percent	Number	Percent
Clinically important.....	215	1.43	660	2.64
Clinically unimportant.....	411	2.74	339	1.36
Total tuberculosis.....	626	4.17	999	4.00

Private and Public General Hospitals, Metropolitan New York

A study of necropsies in private and public general hospitals in metropolitan New York reported by Medlar (14) in 1947 adds to the evidence concerning the numbers of unrecognized cases of tuberculosis in hospitals. The decrease in death rate from tuberculosis during the past 25 years led Medlar to study the validity of the assumption that the incidence of pathologically significant tuberculosis discovered on necropsy would show a similar trend during the same period; as a byproduct of the study, the incidence of unrecognized tuberculosis in general hospitals was considered.

Table 4. *Tuberculosis found on reports of necropsies on patients in metropolitan New York hospitals during 1916-20, and 1940-45; and Medical Examiner's Department of the Borough of Manhattan in 1943*

Necropsy reports studied	Total	Showing evidence of tuberculosis	
		Number	Percent
Total.....	5, 594	898	16. 0
Males.....	3, 657	654	17. 9
Females.....	1, 937	244	12. 6

The material for this study included reports on 14,719 necropsies in private and public general hospitals in metropolitan New York during a 5-year period from 1916-20 and a 6-year period from 1940-45, and also reports on 1,177 necropsies from the Medical Examiner's Department of the Borough of Manhattan for persons who met with sudden death during 1943.

The incidence of significant disease in adults who died in hospitals was found to be approximately the same during the two periods. Pathologically significant tuberculosis seemed to have been recognized clinically in a high proportion of cases below 40 years of age, but in the older age groups, tuberculous infection was frequently not recorded either as the chief or the contributing cause of death even if cavity formation and pathologically active disease were proven. A total of 117 unrecognized cases of active disease were found, 95 percent of them in persons over 50 years of age; no marked difference was found in the incidence in males and females up to 30 years of age, but the rates were higher in males in the older age groups.

Medlar concluded that all persons over 50 years of age, especially males, should have a chest X-ray. Careful study of persons whose X-rays show questionable lesions should be made, including serial roentgenograms and laboratory study, regardless of the impression of importance shown.

The above reports on the incidence of unrecognized tuberculosis in general hospitals indicate that X-ray evidence of tuberculosis has been found in from 2.6 to 8.1 percent of cases admitted to hospitals. Information on the number of proven cases is not presented in all reports, but the rates reported vary from 0.6 to 1.8 percent. These figures are not entirely comparable since the method of classifying cases and the procedures used to determine the diagnosis were not the same in all institutions. Table 5 is presented for general comparison of the incidence of tuberculosis in some of the hospitals studied.

Table 5. *Tuberculosis discovered in 6 general hospitals with routine admission X-ray programs*

Name of hospital and year	Percent of patients with reinfection tuberculosis	Percent of patients with active tuberculosis
University Hospital, Ann Arbor, Mich. (11 days, 1935).....	8.1	1.0
Up-State New York, 14 hospitals (1937-38).....	2.6	1.1
Meyer Memorial Hospital, Buffalo, N. Y. (July 8, 1944-Nov. 12, 1945)....	3.7	1.8
Grasslands Hospital, Valhalla, N. Y. (July 1, 1941-Jan. 1, 1943).....	2.8	.6
Flushing Hospital, Flushing, N. Y. (Aug. 1944-July 1945).....	3.2	.6
University of Chicago clinics, Chicago, Ill. (1942-44).....	4.2	1.4

Programs in Operation

Reports from University Hospital, Ann Arbor, Mich., and the Wisconsin, and New York State departments of health mention some procedures which may be applicable to other hospitals.

University Hospital, Ann Arbor, Mich.

A program of routine X-ray of hospital admissions was instituted in University Hospital in 1941 and has continued without interruption since that time. X-ray equipment is located near the admission desk and an attempt is made to X-ray every person who is admitted. Personnel employed include one technician who operates the machine and processes the films, one radiologist to interpret films (about 30 minutes daily) and to supervise the equipment and operation, and one stenographer to compile and distribute reports. Films are read at a specified hour each day and the reports on questionable cases are sent as soon as possible to the ward on which the patient is located. The cooperation and interest of the hospital staff is mentioned in reports, but no reference is made to referral or to cooperative plans with the health department. In January 1947, a tuberculosis control officer was appointed in University Hospital to have major responsibility for the program and "to expedite more efficient investigation of all hospital registrations, more rapid handling of infectious cases, and prompt and complete X-ray of hospital employees (15)."

Wisconsin State

Filek (16) describes a program begun in Wisconsin in 1946, when two general hospitals were provided with X-ray equipment through the cooperation of the State board of health. The writer indicated that expansion of the program would be limited by the fact that only hospitals with over 300 beds were eligible for full photofluorographic equipment, and Wisconsin had only 3 hospitals of that size. Hospitals with 100 to 300 beds were eligible for partial equipment, however, and the author reported that 4 such hospitals had requested it.

When the program began in Wisconsin, reports on small films only were sent to the State board of health, but space was later provided in the form to include the 14- by 17-inch X-ray film reading as well. Emphasis is placed on the importance of health department participation in the program as a part of the total community tuberculosis program. The health officer and other health department personnel share responsibility for interpretation of the program in the community.

Histories of individuals with questionable lesions are referred to the health department with recommendations for medical and public health nursing follow-up. Interpretation of diagnosis and the education of the patient in the hospital are mentioned as influencing the patient's acceptance or rejection of diagnosis and treatment. Filek suggests that one person in the hospital be made responsible for the program in the institution. He refers to the need for understanding on the part of hospital personnel of the public health facilities and program, and adds that there should be a continuity of interest in the patient if the most effective service is to be rendered to the patient and the community.

New York State

A State-wide program in New York is sponsored by the New York State Department of Health in cooperation with general hospitals; all nonprofit public or private general hospitals are eligible to participate.

Hospitals which have an annual admission rate sufficiently large to guarantee a minimum of 4,000 admission chest X-rays of adults are eligible for the loan of equipment and also for payments of 50 cents for each report of admission X-rays submitted. Hospitals which do not have high enough admission rates to qualify for the loan of equipment may participate by using their own equipment. They receive \$1 for each report submitted. Requests from the larger hospitals are given priority in the loan of equipment.

Hospitals which elect to participate in the program submit a formal application, in which they agree to X-ray the chests of all admitted

patients 15 years of age or over, and of all employees; to provide for interpretation of X-rays; to make no charge for either the initial X-ray or for later X-rays necessary for diagnosis of tuberculosis; to make such X-ray and sputum examinations as may be indicated for persons whose initial X-ray shows definite or suspected tuberculosis; and to permit representatives of the State health department to observe, advise, and consult with the hospital in the program. The application also provides for reporting all X-rays taken under the program, and complying with State regulations for reporting tuberculosis cases.

Before the application is approved, the health officer in whose jurisdiction the hospital is situated works with the hospital representatives on plans for the program. Representatives of the State division of tuberculosis are available for consultation where indicated and may visit the hospital to review technical arrangements before approvals are issued.

The health officer is also charged with responsibility for the follow-up of previously unknown cases of definite or suspected tuberculosis. Care of cases of nontuberculous pathology vary with local policies and procedures. Public health nurses make the necessary visits to arrange for diagnostic services or give patient care.

Hospitals in New York are encouraged to use the services of the local tuberculosis control officer or the staff of the local tuberculosis hospital for the interpretation of films and for consultation on special cases. They are also requested, insofar as possible, to complete the diagnosis before the patient leaves the hospital and are asked to exercise caution "not to disturb patients by isolating them unless there is definite evidence of active tuberculosis."

Discussion

The effectiveness of routine chest X-ray examination of all hospital admissions has been adequately demonstrated. The incidence of tuberculosis has been found to be higher among persons who enter the hospital than among the general population. Considering that approximately 16,000,000 persons are admitted to general hospitals each year, it is evident that a significant number of tuberculosis cases could be found if all 16,000,000 were to have chest X-rays. The advantage to the hospital in protection of personnel, as well as to the community and to the individuals concerned, cannot be discounted.

The fact remains, however, that most patients do not have routine X-rays when they are admitted to general hospitals. Oatway (17) conducted a survey in September 1948 to find out what proportion of the general hospitals in the United States had programs of routine chest X-ray for patients on admission. Information that he gathered from State health departments and other correspondents indicated

that at that time only 247 of the 4,539 general hospitals in this country had programs in action. Oatway found that other hospitals had equipment or plans to start programs, but few hospitals reported that all of their patients were included in these "routine" procedures.

Financial considerations undoubtedly account for the failure of many hospitals to undertake such programs. Help from the State health department in providing X-ray equipment, such as reported by New York and Wisconsin, is a reasonable way to relieve the hospital of part of the cost of a procedure which has public health significance. Oatway found that voluntary groups gave valuable assistance.

Even when the equipment is available, X-raying every patient who is admitted to the hospital gives rise to administrative problems which may deter hospitals from trying such a plan. Not only must a technician be at hand to make the X-rays, but appointments must be scheduled for those patients who cannot, because of acute illness, be X-rayed on admission. The films must be read every day. Records must be kept. Provision must be made for whatever services are needed to establish a diagnosis. Patients must be notified of the results—sometimes after they have left the hospital. Interpretation must be made to patients, so that they will understand the follow-up that may be necessary. Appropriate reports must be sent to the health department.

These new duties require the understanding and collaboration of the hospital staff. In some larger hospitals it may be necessary to add new persons to the staff, but whether that is done or not, the admission chest X-ray program cannot be carried on in the radiography department alone. It requires the conscious effort of everyone responsible for service to patients.

Hospitals which operate chest X-ray programs as part of their routine admission procedure, and have dealt with the administrative perplexities, could do a service to tuberculosis case finding by sharing experience with others.

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Studies on Experimental Histoplasmosis

I. A Report on Intracerebral Inoculations of Male dba Line 1 Mice

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One of the constantly recurring problems in the study of histoplasmosis is the lack of a laboratory animal which is consistently susceptible to the causative organism, *Histoplasma capsulatum* (1-6). Tager and Liebow (4) have pointed out, however, that in most of the studies reported in the literature, such factors as age, strain of animal, weight at inoculation, and other causes of variation have not been adequately controlled.

With this in mind, the authors investigated the susceptibility of a number of strains of mice by various routes of inoculation. In addition, several strains of the fungus were studied. In the present report, it will be demonstrated that uniformly successful results can be obtained by inoculating a specified strain of mice by a single route of injection utilizing a particular strain of *Histoplasma*.

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Materials and Procedures

The mice used were males of the dilute brown strain, dba line 1, obtained from the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine. Mice 4 to 5 weeks old, weighing 10 to 18 grams, were used throughout. Altogether, 7 experiments were carried out over a period of 10 months; a total of 272 animals were studied. Each mouse was inoculated with 0.02 ml. of a given dilution of a saline suspension of the yeast phase of the fungus or 0.02 ml. of saline alone, intracerebrally. The strain of *Histoplasma* employed was obtained in 1948 from Dr. Norman F. Conant, Duke University School of Medicine. He stated that it had been isolated from a fatal case of human histoplasmosis observed in Cincinnati in 1947 by Dr. Isaac Ruckman (?). Since its receipt by the authors, this culture, has been maintained in the yeast phase by a series of consecutive subcultures transferred on brain heart infusion blood agar slants, sealed with paraffin and incubated at 37° C., at intervals sufficiently close together to maintain viable organisms.

The inoculum was prepared from 5-day-old yeast phase cultures of the fungus. The growth was washed from the slants with sterile physiological saline. One cc. of this suspension was centrifugalized at 2,000 r.p.m. for 20 minutes to determine the original concentration of the suspension. The remainder was then adjusted in order to produce a 1/100 suspension of organisms in physiological saline.

The mice were weighed on the date of inoculation and at intervals thereafter up to the 30th day after inoculation, at which time any surviving mice were sacrificed. Complete autopsies were performed on all mice, both those that died spontaneously and those that were sacrificed.

At autopsy a portion of the brain and a portion of the spleen were removed from each mouse for the preparation of smears and cultures. Smears were stained with Giemsa's stain. Cultures were made on brain-heart infusion blood and potato dextrose agar plates, to each of which had been added 40 units of penicillin and 40 units of streptomycin per ml. of media. All cultures were incubated at room temperature. In addition, sections prepared from Zenker-fixed material and stained with hematoxylin and eosin and Goodpasture's stain were prepared from all tissues from all animals in four of the seven experiments.

After inoculation of the mice, serial dilutions were prepared from the 1/100 suspension of the organisms. Two-hundredths of a milliliter of a 1/1,000,000 and/or 1/10,000,000 dilution were then cultured on each of 10 brain heart infusion blood agar plates which were incubated at room temperature. From the colony counts obtained from these plates, an approximation of the number of viable organisms actually injected was calculated. While it might have

seemed advisable to calculate the dosage of organisms by direct hemacytometer count, this method gives no idea as to the viability of the organisms being introduced. Since, in any infection, the viable organisms are most important, it was felt that plate counts would be a much more accurate method of estimating the number of organisms capable of producing infection than the total number of organisms injected.

Findings

The dosages employed and the percentage of fatalities which followed are presented separately for each experiment in table 1. It should be pointed out that in this series of seven experiments, in every

Table 1. *Results, in terms of mortality, obtained in a series of experiments in which male dba line 1 mice were injected intracerebrally with saline suspensions of the yeast phase of a single strain of Histoplasma capsulatum at different dose levels*

Experiment number	Date of injection	Dilution employed	Estimated dose per injection in thousands of organisms	Animals				
				Total number (100 per cent)	Died before 30th day after injection		Sacrificed on 30th day after injection	
					Number	Percent	Number	Percent
I.....	Jan. 18, 1949	1/100.....	319	3	3	100.0	-----	-----
II.....	Mar. 17, 1949	1/100.....	339	5	4	80.0	1	20.0
		1/200.....	169	5	5	100.0	-----	-----
		1/400.....	85	5	5	100.0	-----	-----
		1/800.....	42	5	5	100.0	-----	-----
		Saline.....	0	5	-----	-----	5	100.0
III ¹								
IV.....	May 27, 1949	1/100.....	88	5	5	100.0	-----	-----
		1/200.....	44	6	6	100.0	-----	-----
		1/400.....	22	6	6	100.0	-----	-----
		1/800.....	11	6	4	66.7	2	33.3
		1/1600.....	6	6	4	66.7	2	33.3
		1/3200.....	3	6	1	16.7	5	83.3
		1/6400.....	1	6	4	66.7	2	33.3
		Saline.....	0	4	-----	-----	4	100.0
V.....	June 16, 1949	1/200.....	263	5	5	100.0	-----	-----
		1/400.....	131	5	5	100.0	-----	-----
		1/800.....	66	5	5	100.0	-----	-----
		1/1600.....	33	5	-----	-----	5	100.0
		Saline.....	0	5	-----	-----	5	100.0
VI.....	July 22, 1949	1/500.....	76	9	3	33.3	6	66.7
		1/1000.....	38	10	4	40.0	6	60.0
		1/2000.....	19	10	2	20.0	8	80.0
		Saline.....	0	7	-----	-----	7	100.0
VII ²								
VIII.....	Sept. 28, 1949	1/100.....	2,177	23	23	100.0	-----	-----
		1/400.....	541	23	23	100.0	-----	-----
		1/800.....	272	23	23	100.0	-----	-----
		1/1600.....	136	23	23	100.0	-----	-----
		Saline.....	0	9	-----	-----	9	100.0
IX.....	Nov. 14, 1949	1/100.....	1,546	10	10	100.0	-----	-----
		1/600.....	257	10	10	100.0	-----	-----
		1/3600.....	43	10	10	100.0	-----	-----
		Saline.....	0	7	-----	-----	7	100.0
Total number of animals ³				235	198	84.3	37	15.7
{Injected with a suspension of <i>Histoplasma</i>				37	-----	-----	37	100.0
{Injected with saline alone.....				-----	-----	-----	-----	-----

¹ No dba males were included in this experiment.

² All animals in this experiment died within a week of injection immediately following a fire in the laboratory.

³ 3 animals, 2 injected with a suspension of *Histoplasma* and 1 with saline alone, were not included in the above tabulation, because death intervened within 18 hours of the time of injecting.

group injected with *Histoplasma*, regardless of dose, one or more animals died spontaneously. Furthermore, in order to provide a control group, some animals were injected with saline alone in each of the last six experiments; none of these died.

The results of these experiments were then pooled; and, after examination of the data, appropriate groupings by dose were made. Scrutiny of the results following various doses indicated that any injection of 500,000 or more organisms gave effects so similar that all doses of this magnitude were combined. However, for various reasons, which will be explained later, it became apparent that the animals in experiments V and VI did not behave in a manner exactly similar to those in the other experiments. Therefore, the results of these two experiments will be presented separately. The pooled results of the remainder of the experiments, with respect to mortality, are presented in table 2.

Table 2. *Comparative mortality observed among male dba line 1 mice within 30 days of intracerebral injection with varying doses of Histoplasma capsulatum*

Estimated dose per injection in thousands of organisms	Total number (100 percent)	Died before 30th day after injection		Sacrificed on 30th day after injection	
		Number	Percent	Number	Percent
Over 500.....	56	56	100.0	-----	-----
400-499.9.....	-----	-----	-----	-----	-----
300-399.9.....	8	7	87.5	1	12.5
200-299.9.....	33	33	100.0	-----	-----
100-199.9.....	28	28	100.0	-----	-----
20-99.9.....	37	37	100.0	-----	-----
Subtotal.....	162	161	99.4	1	.6
1-19.9.....	24	13	54.2	11	45.8
Total.....	186	174	93.5	12	6.5
0 (saline only).....	25	-----	-----	25	100.0

In this series of experiments, excluding V and VI, any dose of 20,000 or more organisms of this strain of *Histoplasma* suspended in saline and administered to dba line 1 males, 4 to 5 weeks of age, by the intracerebral route, resulted in fatality in practically 100 percent of the cases. Of 162 mice so treated, 161, or 99.4 percent, died spontaneously before the 30th day after injection; only 1 mouse lived until the sacrifice date. On the other hand, of the 24 animals that received less than 20,000 organisms, only 13, or 54.3 percent, died. Furthermore, from table 1, it can easily be seen that this did not depend on the results of a single low dose employed in one experiment alone. In every group receiving less than 20,000 organisms, more than one animal survived.

There appears to be some further evidence that a dose of approximately 20,000 organisms of this strain of *Histoplasma* under the experimental conditions imposed is not far from the minimal lethal dose. For example, of the six animals which received this dose, two

survived beyond the 20th day. In contrast to this, of the 21 animals receiving the next highest dose (approximately 43,000 organisms), only 1 animal survived past the 14th day. This animal died on the 18th day. Thus it would appear highly probable that intracerebral injection of 40,000 viable organisms of a virulence comparable to that of this strain is regularly lethal for dba line 1 male mice.

Another approach which is frequently employed in attempting to assess the lethal effect of various doses of an organism on a given animal is a determination, for each dose level, of the time at which a specified proportion of the animals may be expected to die. Cumulative death curves by day are given in table 3 for each dose. Although it is apparent that differences do exist, even among the dose groups which eventually produced 100 percent fatality, it can readily be seen that the difference between those receiving less than 20,000 organisms and any dose higher than this is far greater than any of the differences among groups which received higher doses. Since only 54 percent of those receiving less than 20,000 organisms died, the only variable which can be used for comparison in this regard is the day on which it

Table 3. Cumulative mortality observed among male dba line 1 mice within 30 days of intracerebral injection with varying doses of *Histoplasma capsulatum*

Day during which death occurred	Estimated dose per injection in thousands of organisms ¹											
	500 and over		300-399.9		200-299.9		100-199.9		20-99.9		Under 20	
	Cumulative spontaneous deaths											
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
3	1	1.8	1	12.5								
4	8	14.3	2	25.0	1	3.0	1	3.6	3	8.1		
5	16	28.6	2	25.0	4	12.1	2	7.1	7	18.9	5	20.8
6	35	62.5	2	25.0	11	33.3	6	21.4	8	21.6	7	29.2
7	45	80.4	5	62.5	20	60.6	8	28.6	12	32.4	9	37.5
8	51	91.1	5	62.5	27	81.8	14	50.0	17	45.9	9	37.5
9	55	98.2	6	75.0	31	93.9	19	67.9	25	67.6	9	37.5
10	56	100.0	7	87.5	32	97.0	25	89.3	31	83.8	9	37.5
11	56	100.0	7	87.5	33	100.0	27	96.4	33	89.2	10	41.7
12	56	100.0	7	87.5	33	100.0	27	96.4	33	89.2	10	41.7
13	56	100.0	7	87.5	33	100.0	27	96.4	34	91.9	11	45.8
14	56	100.0	7	87.5	33	100.0	27	96.4	34	91.9	11	45.8
15	56	100.0	7	87.5	33	100.0	27	96.4	34	91.9	11	45.8
16	56	100.0	7	87.5	33	100.0	27	96.4	34	91.9	11	45.8
17	56	100.0	7	87.5	33	100.0	27	96.4	34	91.9	11	45.8
18	56	100.0	7	87.5	33	100.0	28	100.0	35	94.6	11	45.8
19	56	100.0	7	87.5	33	100.0	28	100.0	35	94.6	12	50.0
20	56	100.0	7	87.5	33	100.0	28	100.0	36	97.3	12	50.0
21	56	100.0	7	87.5	33	100.0	28	100.0	37	100.0	12	50.0
22	56	100.0	7	87.5	33	100.0	28	100.0	37	100.0	12	50.0
23	56	100.0	7	87.5	33	100.0	28	100.0	37	100.0	12	50.0
24	56	100.0	7	87.5	33	100.0	28	100.0	37	100.0	12	50.0
25	56	100.0	7	87.5	33	100.0	28	100.0	37	100.0	13	54.2
26	56	100.0	7	87.5	33	100.0	28	100.0	37	100.0	13	54.2
27	56	100.0	7	87.5	33	100.0	28	100.0	37	100.0	13	54.2
28	56	100.0	7	87.5	33	100.0	28	100.0	37	100.0	13	54.2
29	56	100.0	7	87.5	33	100.0	28	100.0	37	100.0	13	54.2
30	56	100.0	7	87.5	33	100.0	28	100.0	37	100.0	13	54.2
Total mice injected	56	100.0	8	100.0	33	100.0	28	100.0	37	100.0	24	100.0

¹ No mice were given estimated doses of 400-499.9 thousand organisms.

was observed that 50 percent of the animals had died. As a matter of fact, the time required to kill 50 percent of the mice follows a very clearly defined pattern from high to low dosage with a marked change in the survival time between those receiving 20,000 or more organisms and those receiving less than this amount. Fifty percent of those animals receiving 500,000 or more organisms were dead by the end of the 7th day. Among those receiving 300,000 to 399,999 organisms, and also the next lower dose, this point was reached between the 7th and 8th days. At the dose level of 100,000 to 199,999, the mortality reached 50 percent between the 8th and 9th days; and in the next lowest group (the lowest completely lethal dose) 50 percent died by the 10th day. However, when doses of under 20,000 organisms were given, it was not until the 19th day that 50 percent of the animals were dead.

It was noted throughout the course of the experiments that, even though the mice used were inbred and all of the same age, the weights of the individual animals at the time of inoculation varied considerably. Further, the extent of the variation and the average weights differed from one lot of animals to another. For example, the weights of the mice employed in experiment IV ranged from 12 to 19 grams, with well over one-half of the animals weighing 16 grams or more; whereas in experiment VIII the weights of the animals ranged from 10 to 17 grams with over one-half of the animals weighing 13 grams or less. In still another experiment, on the other hand, the mice varied over a comparatively short range (11 to 16 grams) with the greatest number occurring at about the midpoint, 14 grams.

Unfortunately, the percentage distribution of the mice by weight

Table 4. *Comparison of observed mortality among male dba line 1 mice given intracerebral injections of saline alone, of Histoplasma capsulatum in doses of less than 20,000 organisms, and of Histoplasma capsulatum in doses of 20,000 or more organisms according to weights of animals at time of injections*

Weight in grams at time of injection	Saline alone, ¹ total number (100 percent)	Under 20,000 organisms				20,000 organisms and over					
		Total number (100 percent)	Died before 30th day after injection		Sacrificed on 30th day after injection		Total number (100 percent)	Died before 30th day after injection		Sacrificed on 30th day after injection	
			Number	Per- cent	Number	Per- cent		Number	Per- cent	Number	Per- cent
9.0-9.9	1										
10.0-10.9	1							8	8	100.0	
11.0-11.9	1							18	18	100.0	
12.0-12.9	1	1			1	100.0		22	22	100.0	
13.0-13.9	6	2	1	50.0	1	50.0		34	34	100.0	
14.0-14.9	4	2	1	50.0	1	50.0		36	36	100.0	
15.0-15.9	5	3	2	66.7	1	33.3		20	20	100.0	
16.0-16.9	1	9	5	55.6	4	44.4		10	9	90.0	1
17.0-17.9	4	6	3	50.0	3	50.0		9	9	100.0	
18.0-18.9	1	1	1	100.0				4	4	100.0	
19.0-19.9								1	1	100.0	
Total number of animals...	25	24	13	54.2	11	45.8		162	161	99.4	.6

¹ All mice given injections of saline alone were sacrificed on the 30th day.

at time of inoculation was not the same for those animals that received under 20,000 organisms and those that received 20,000 or more organisms. However, it can be seen from table 4 that there is no evidence that this introduced a bias which would invalidate the mortality rates quoted for these two groups. For starting weights 13, 14, 15, 16, and 17 grams, respectively, more than one mouse was included in both dose groups. In every case those receiving 20,000 or more organisms showed a higher death rate than animals receiving less than 20,000, and these differences are statistically significant. Still more important is the fact that the differences in death rates were of the same order of magnitude regardless of initial weight.

All animals were examined at autopsy for gross lesions. Sections were prepared for microscopic examination from the tissues of the 61 mice in experiments II and IV. However, through clerical error, the sections prepared from one of these mice were not available for study.

Although in no animal in any experiment were any gross lesions noted, most of the animals from which tissue sections were prepared showed lesions in the brain, liver, and spleen. In the brain, a granulomatous meningitis of varying intensity was almost a constant finding; in a few instances the process extended into the spinal cord. In the liver the typical lesion observed was patchy necrosis of parenchymal cells, and in the spleen, a reticulo-endothelial hyperplasia which

Table 5. Findings on microscopic examination of tissue sections taken at autopsy from male dba line 1 mice injected intracerebrally with varying doses of *Histoplasma capsulatum* or with saline only

Estimated dose per injection in thousands of organisms	Total number of mice (100 per-cent)	Mice in which lesions were—				Mice in which organisms were—					
		Observed		Not observed		Present		Questionably present		Absent	
		Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
DIED SPONTANEOUSLY											
Under 20.....	12	12	100.0	-----	-----	11	91.7	1	8.3	-----	-----
20-99.9.....	27	24	88.8	3	11.2	24	88.8	-----	-----	3	11.2
100-199.9.....	5	5	100.0	-----	-----	5	100.0	-----	-----	-----	-----
200-299.9.....	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
300-399.9.....	4	4	100.0	-----	-----	4	100.0	-----	-----	-----	-----
SACRIFICED											
Under 20.....	11	7	63.6	4	36.4	3	27.3	3	27.3	5	45.4
20-99.9.....	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
100-199.9.....	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
200-299.9.....	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
300-399.9.....	1	-----	-----	1	100.0	-----	-----	-----	-----	1	100.0
CONTROL ANIMALS											
Saline alone.....	9	-----	-----	9	100.0	-----	-----	-----	-----	9	100.0

¹ There were no sections of liver in 2 mice and no section of spleen in 1 mouse.

ranged from slight to marked. The only other organ in which abnormalities were noted was the heart. Tiny areas of fibrosis were seen in the heart of one mouse that had been injected with less than 20,000 organisms and which was sacrificed on the 30th day. Necrosis of the myocardial fibrils was observed in one mouse injected with 20,000 to 99,999 organisms, which died on the 11th day after injection. Similar myocardial necrosis was seen in one control animal.

A comparison of the proportion of animals in which lesions could be seen on microscopic examination among 48 mice which died with that among 12 which were sacrificed shows that 45 of the 48 had lesions as compared with 7 of the 12. All 3 of the former group which showed no lesions had received an injection of 20,000 to 99,999 organisms. Each of them had shown a loss in weight comparable to others in the group and positive cultures were obtained from tissues removed at autopsy of two. (Cultures of the brain and spleen of the remaining animal were contaminated.) One of the five mice which showed no lesions in the latter group had received an injection of 300,000 to 399,999 organisms. Although *Histoplasma* was recovered from this mouse, its weight curve suggested that infection may have occurred but that the animal had recovered spontaneously.

In one dose group, the number of animals that died was approximately equal to the number sacrificed, so that a comparison of the severity of the lesions was possible. As was to be expected, the degree of severity of the lesions was greater among those that died spontaneously than among those that were sacrificed, even though the number of animals exhibiting lesions in the three major sites did not differ widely; and, in practically all animals that showed lesions microscopically, the brain, liver, and spleen were all involved.

Among 48 mice which died, 45 had lesions which could be seen on microscopic examination. In contrast, only 7 of the group of 12 mice which was sacrificed showed lesions.

As has already been mentioned, all mice were weighed at the time of injection and periodically thereafter until they died or were sacrificed. The interval between weighings was made shorter in the later experiments with the hope of obtaining a more precise index of the effect of various doses of *Histoplasma* on the animal. This possibility was suggested by the very obvious difference between the controls and the animals injected with the fungus, the former progressively gaining and the latter losing weight, at least in the days immediately following injection.

It was noted, however, that the rate of weight loss in the experimental animals was to some extent influenced by the initial weights, in that the initially heavier mice lost not only an absolutely greater amount but also a larger proportion of their initial weight. Because of the differences in initial weights among the various dose groups, it was necessary to take this relationship into account in comparing the

patterns of weight change from one group to another. To accomplish this, the line of regression of percent weight loss on initial weight was estimated for each day after injection on which animals were weighed. The observed percent lost by each mouse was then adjusted by means of the slope of this line to correspond to that expected of an animal initially weighting 14 grams. An adjusted weight in grams was determined from this percentage.

The means of the adjusted weights of the mice in each dose group on each day after treatment are given separately in table 6 for animals which died spontaneously and for those which were sacrificed. Except for controls and the sacrificed animals in the group receiving less than 20,000 organisms, values are not given beyond the 11th day because of the small number surviving.

Examination of table 6 immediately reveals the sharp contrast between the rising weights of control animals and the decline of those in the experimental groups. Differences by dose among the various experimental groups, however, are less clear. The loss of weight continued throughout the first 8 to 10 days at about the same rate regardless of dose. There is some indication of a delay in the start of this loss among the mice that survived to be sacrificed following the dose of less than 20,000 organisms, but the evidence is not overwhelming. There is also some slight appearance of an increasing rate of loss of weight with increasing dose, but this is even less marked and could not be demonstrated statistically. However, it is worth noting that the decrease in mean weight within 8 days was more than 4 grams in every group except that sacrificed 30 days after doses of less than 20,000 organisms. In the latter group, the mean weight

Table 6. *Mean weights¹ in grams of groups of male dba line 1 mice at the time of and following intracerebral injection with Histoplasma capsulatum*

Days after injection	Died before 30th day after injection										Sacrificed on 30th day after injection			
	Estimated dose per injection in thousands of organisms													
	Less than 20		20-99.9		100-199.9		200-299.9		500 or more		Less than 20		Saline alone	
	Number of mice	Mean adjusted weight	Number of mice	Mean adjusted weight	Number of mice	Mean adjusted weight	Number of mice	Mean adjusted weight	Number of mice	Mean adjusted weight	Number of mice	Mean adjusted weight	Number of mice	Mean adjusted weight
0-----	13	16.22	27	15.84	23	12.97	33	13.82	56	13.13	11	15.92	28	13.47
2-----			10	12.13	23	12.03	33	12.46	56	11.63			28	13.51
4-----	13	14.65	27	14.21	23	11.77	33	12.30	55	10.81	11	15.75	32	14.16
6-----			19	11.27	26	9.25	29	9.64	43	8.63			33	14.33
7-----	6	11.32	11	10.49							11	13.32		
8-----			6	9.85	17	8.83	16	9.06	10	8.28			28	14.39
10-----					7	7.94							23	14.31
11-----	4	10.90									11	12.74		

¹ Weights adjusted for differences in rate of loss associated with differences in initial weights.

loss within 8 days was 2.6 grams. The controls gained an average of 0.9 grams within the same period of time. This observation suggests an additional criterion whereby the presence or absence of infection can be judged.

It has been previously noted that the animals in experiments V and VI did not behave in a manner similar to the others. For example, in experiment V (table 1), while each of the animals which received a dose of 100,000 to 299,999 died, 2 survived to the 22d and 23d day, respectively; whereas, among the animals that received this dose in other experiments in the series, only one animal survived beyond the 12th day, and it died on the 18th day (table 3). Furthermore, of 10 animals in this experiment which received a dose of 20,000 to 99,999 organisms, only 5, or 50 percent, died spontaneously, in contrast to the 100 percent mortality observed following this dose in the other experiments. Thus it appeared that some loss of virulence in the strain of *Histoplasma* being used was occurring at this time.

This phenomenon became even more pronounced in experiment VI. Of 19 animals injected with 20,000 to 99,999 organisms, 7 died spontaneously. This constitutes only 36.8 percent of the group. The length of time before death intervened was also extended; for example, spontaneous death occurred in one mouse on the 27th day and in one, on the day when it would have been sacrificed.

The distribution of the animals by initial weight in experiment VI differed widely from that of the animals receiving comparable doses in the other experiments. Unfortunately the difference is so great in the animals receiving under 20,000 organisms that no comparison can be made with regard to mortality rates among mice having the same initial weight. However, the overlap in initial weights in animals receiving 20,000 to 99,999 organisms permits such a comparison, and

Table 7. Comparison of observed death rates among male dba line 1 mice in experiments V and VI

Experiment V						Experiment VI					
Estimated dose per injection in thousands of organisms	Total number of animals (100 percent)	Died before 30th day after injection		Sacrificed on 30th day after injection		Estimated dose per injection in thousands of organisms	Total number of animals (100 percent)	Died before 30th day after injection		Sacrificed on 30th day after injection	
		Number	Percent	Number	Percent			Number	Percent	Number	Percent
200-299.9-----	5	5	100.0	-----	-----	200-299.9-----	-----	-----	-----	-----	-----
100-199.9-----	5	5	100.0	-----	-----	100-199.9-----	-----	-----	-----	-----	-----
20-99.9-----	10	5	50.0	5	50.0	20-99.9-----	¹ 19	7	36.8	12	63.2
Less than 20-----	-----	-----	-----	-----	-----	Less than 20-----	10	2	20.0	8	80.0
Total-----	20	15	75.0	5	25.0	Total-----	29	9	31.0	20	69.0
Saline alone-----	5	-----	-----	5	100.0	Saline alone-----	5	-----	-----	5	100.0

¹ 1 animal died during inoculation.

there is no evidence to indicate that the high survival rates observed in experiment VI were dependent upon the comparatively low initial weights of the animals employed.

This apparent loss of virulence in the strain of the fungus employed seems to have been temporary; since, in experiment IX (table 1), a dose of approximately 43,000 organisms again killed 10 of 10 animals, or 100 percent, with none of these animals surviving beyond the 12th day after injection.

At autopsy no gross abnormalities were noted in any of the animals in experiments V and VI. Microscopically there appeared to be little or no difference in experiment V between sacrificed animals and those dying spontaneously in the percentage which showed lesions, in the type and location of the lesions, or in the number in which *Histoplasma* was demonstrated. The number of animals, however, was too small to permit statistically valid comparison. This was also true in experiment VI. But the mice that were sacrificed in experiment VI showed fewer lesions and the organism was not seen in as many mice.

When the degree of severity of the lesions is considered, the animals in experiment V appeared to follow much the same pattern as those in previous experiments. However, among the sacrificed animals the number showing no lesions was greater than in previous experiments. Since the number of animals in this series was small, this finding is probably of little importance in itself, but none of the five animals in this group showed any moderate to severe lesions. Among the animals

Table 8. Mean weights¹ in grams of male dba line 1 mice injected intracerebrally with *Histoplasma capsulatum* in experiments V and VI

Days after injection	Experiment V								Experiment VI									
	Died before 30th day after injection								Sacrificed on 30th day after injection		Died be- fore 30th day after injection				Sacrificed on 30th day after injection			
	Estimated dose, in thousands of organisms																	
	20-99.9		100-199.9		200-299.9		20-99.9		20-99.9		Less than 20		20-99.9					
Number of mice	Mean ad- justed weight	Number of mice	Mean ad- justed weight	Number of mice	Mean ad- justed weight	Number of mice	Mean ad- justed weight	Number of mice	Mean ad- justed weight	Number of mice	Mean ad- justed weight	Number of mice	Mean ad- justed weight	Number of mice	Mean ad- justed weight			
0	5	15.44	5	16.50	5	16.08	5	16.34	7	11.93	8	10.32	12	12.08				
2	5	15.94	5	15.92	5	16.04	5	15.76	7	11.43	8	11.21	12	12.31				
4	5	14.84	5	14.10	5	15.70	5	16.16	7	10.80	8	9.01	12	11.50				
6	5	11.18	5	11.10	4	9.20	5	12.16	7	9.56	8	8.02	12	9.82				
8	5	10.98	4	8.94	4	9.10	5	11.18	5	7.96	8	7.44	12	8.79				
10									5	7.34	8	7.84	12	8.68				
12	4	10.38					5	10.90	4	8.10	8	8.00	12	8.92				

¹ Weights adjusted for differences in rate of loss associated with differences in initial weights.

in experiment VI this tendency toward a milder course of the disease was apparent in both the animals that died spontaneously and those that were sacrificed.

In experiment V there was a loss of weight following injection with *Histoplasma* which was very similar in magnitude to that observed in the other experiments, the mean decrease on the 8th day being more than 4 grams in all dose groups. It is noteworthy, however, that the decline in weight was generally delayed until after the 4th day. Many individual animals and one dose-group average showed slight gains on the 2d day.

In experiment VI, the weight loss was less both in magnitude and in rate than in any other experiment. The mean decrease on the 8th day was less than 4 grams in all dose groups, but the delay in onset was not as sharply defined as in experiment V. It should be noted that, as a group, the mice in experiment VI were the smallest used, but the tendency of small animals to lose less is offset by the weight adjustment utilized.

It is interesting to note that the pattern of the weight changes in experiment VI more closely resembles that observed in the pooled group of sacrificed animals receiving less than 20,000 organisms in the other experiments than it does that of animals which died spontaneously after any dose. The trend found in experiment V is in some ways intermediate between that in VI and that in the higher dose groups of other experiments. These observations are consistent with the hypothesis that a temporary loss of virulence was occurring during the period throughout which experiments V and VI were performed.

Histoplasma was recovered from the brain and/or spleen of each of the 235 animals except 3 in experiments I through IX. All cultures from each of these three animals were overgrown with contaminants.

Summary of Findings

1. In seven experiments, covering a period of 10 months, 235 male dba line 1 mice, 4 to 5 weeks old, were injected intracerebrally with various doses of a specified strain of *Histoplasma capsulatum*. In each of the last six experiments a group of animals was injected with saline alone to serve as controls. Altogether there were 37 control animals.

2. The results are pooled except for two experiments in which there appeared to be a temporary loss of virulence in the strain of the fungus employed.

3. Appropriate dose groupings revealed that all except 1 animal of 162 given more than 20,000 organisms (estimated by means of a plate count of the inoculum) died spontaneously before the 30th day after injection; whereas, this was true of only 13 of 24 given less than

this dose. None of the control animals died spontaneously.

4. Fifty percent of the mice injected with 20,000 or more organisms died between the 7th and 10th day following injection, the survival time increasing with decreasing dose. Fifty percent of the mice injected with less than this number of organisms survived at least until the 19th day.

5. No animal showed any gross lesions at autopsy.

6. On microscopic examination of tissues at autopsy, lesions were found in all except 3 animals that died spontaneously and in the majority (9 of 12) of those sacrificed.

7. The lesions consisted of a granulomatous meningitis in the brain, necrosis of the liver parenchyma, and a reticulo-endothelial hyperplasia of the spleen.

8. During the 8 days following intracerebral injection of *Histoplasma*, loss of weight occurred regularly. Control animals injected with saline showed a progressive gain in weight during the same period of time.

9. The rate of loss among animals which died spontaneously was similar regardless of dose, the mean weight loss being more than 4 grams in all groups.

10. The two experiments that were performed during the time over which there appeared to be a temporary loss in the virulence of the organisms are reported separately in the text.

11. *Histoplasma* was recovered from the tissues of all animals in the entire series of 235 except 3. All cultures from these three animals were overgrown with contaminants.

Discussion

Recognition of the need for a laboratory animal which could be shown to be fairly uniformly susceptible to *Histoplasma capsulatum* led to the present series of experiments. Our research indicates that such an animal has been found. It immediately follows that a base line for the measurement of the virulence of any strain of the fungus can be established.

The establishment of such a base line should make possible various studies concerning the organism which have heretofore not been possible. Among these are: (1) comparison of the virulence of one strain of *Histoplasma* with that of another; (2) comparison of the susceptibility of various strains of mice; (3) investigation of long-term, continuing or temporary changes in virulence in a given strain of the fungus which has been kept alive through a series of cultures over a period of time; (4) study of changes in the virulence in a given strain of the organism following serial passage through an animal host; and (5) possibly, comparison of the effects of various chemotherapeutic agents.

For example, with regard to possible temporary changes in virulence when the fungus has been maintained through a series of subcultures, in the series of experiments being reported there appeared to be a loss of virulence in two of the experiments which was subsequently regained in succeeding experiments. Studies should be undertaken to determine whether changes of this kind occur in all strains of *Histoplasma* and whether it is cyclical or random from the point of view of time.

Also, more intensive work should be directed toward finding, within the closest possible range of error, doses of the organism which can be expected to produce given results.

Another point for discussion is the method whereby the estimated dose was determined. All too frequently, there is reported only the dilution of the suspension which assumes implicitly that one dilution of 1-100 equals any other dilution of 1-100 with respect to the number of viable organisms. That this is not necessarily true is demonstrated by the present experiments in which it was shown that a constant dilution could give highly variable numbers of viable organisms as estimated by a plate count.

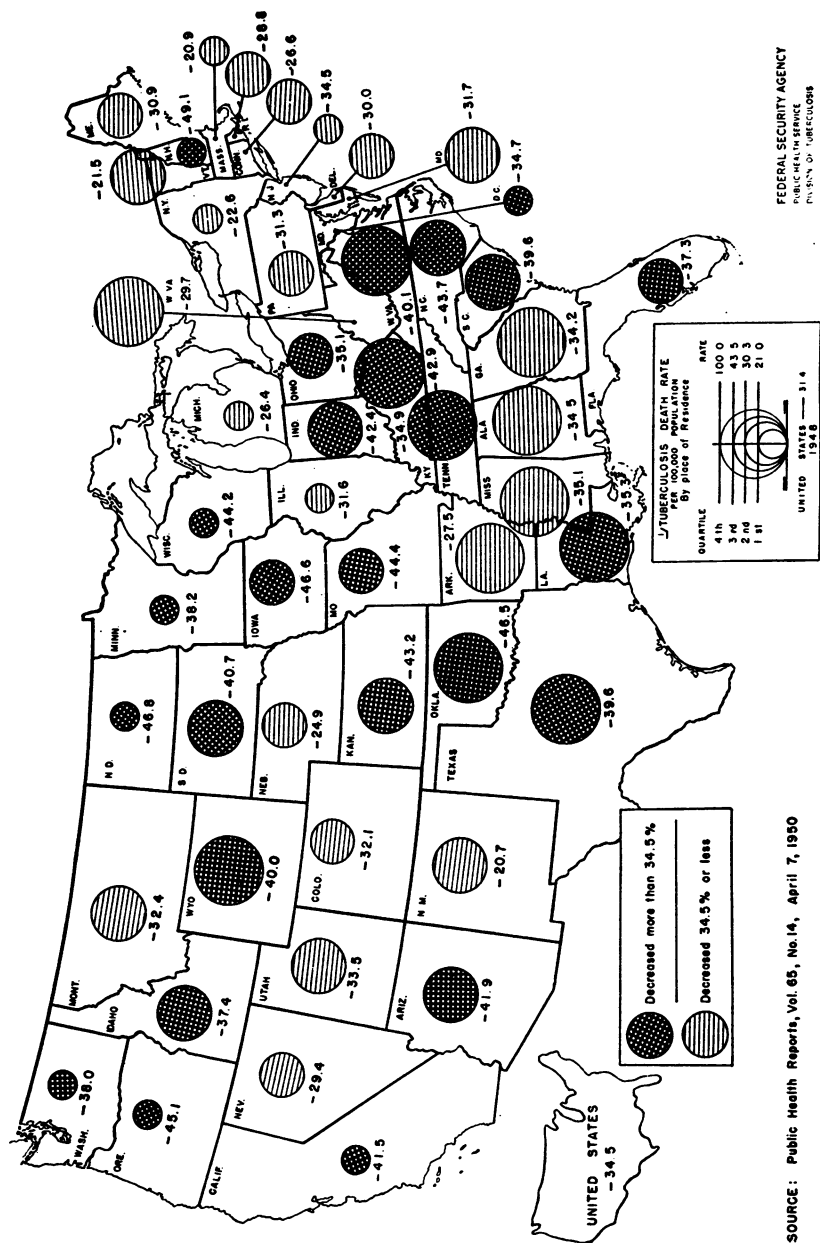
Conclusions

From the foregoing it can be concluded that male dba line 1 mice, 4-5 weeks of age, are suitable animals for laboratory study of *Histoplasma capsulatum*. Given sufficient doses, they are uniformly susceptible to the organism, and the time of survival can be regulated by the dosage.

NOTE: Since this report was received for publication, the successful inoculation of white Swiss mice (Bagg strain) by the intraperitoneal injection of very large doses of the yeast phase of *Histoplasma* suspended in mucin has been reported. (Campbell, C. C. and Saslaw, S: Use of mucin in experimental infections of mice with *Histoplasma capsulatum*. Proc. Soc. Exper. Biol. and Med. **73**: 469-472 (1950).) Our studies employing mucin, various routes of administration, and various strains of mice, and concerning the relative virulence of different strains of *Histoplasma* will be reported later.

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INCIDENCE OF DISEASE

No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring

UNITED STATES

REPORTS FROM STATES FOR WEEK ENDED MAY 13, 1950

Influenza

For the current week in the Nation, reported cases of influenza continued to decrease from the preceding week but remained above the 5-year (1945-49) median. For the current week, 2,492 cases of influenza were reported as compared with 3,399 for the previous week, 1,317 for the corresponding week a year ago, and the 5-year median of 1,221.

The cumulative total for the first 19 weeks of the year was 236,302 which may be compared with the corresponding total of 68,737 for the same period last year and 292,674 for 1947, the highest on record for the past 5 years. The corresponding 5-year median was 131,466.

Other Reportable Diseases

Reported incidence of whooping cough continued to increase for the current week over the previous week, from 2,691 to 2,867 cases. The total for the corresponding week last year was 1,054 and the 5-year (1945-49) median was 1,965. The cumulative total for the first 19 weeks of the year was 49,977 which may be compared with the corresponding total of 19,094 for the same period last year and 51,914 for 1947, the highest on record for the past 5 years. The corresponding 5-year median was 40,341.

Reported incidence of tularemia increased from 17 last week to 24 cases for the current week, the highest on record for the corresponding week in the last 5 years. For the first 19 weeks of the year the cumulative total was 387 which may be compared with 458 cases for the same period last year and 590, the highest on record for the past 5 years. Arkansas reported 10 of the 24 cases for the current week and Texas reported 4 cases.

There was an increase in reported cases of acute poliomyelitis in the Nation from 72 cases last week to 102 cases for the current week. The total for the week includes 28 cases in California (from 14 to 28) and 38 cases in Texas (from 28 to 38).

One case of anthrax was reported in Pennsylvania, 1 case of smallpox was reported in Nevada, and 74 cases of salmonellosis were reported in California.

Telegraphic case reports from State health officers for week ended May 13, 1950
(Leaders indicate that no cases were reported)

Division and State	Diphtheria	Encephalitis, infectious	Influenza	Measles	Meningitis, meningococcal	Pneumonia	Polio-myelitis	Rocky Mountain spotted fever	Scarlet fever	Small-pox	Tularemia	Typhoid and paratyphoid fever ¹	Whooping cough	Rabies in animals
NEW ENGLAND														
Maine.....			81	14	1	8			13				16	
New Hampshire.....				27		5			8				8	
Vermont.....				11					3				30	
Massachusetts.....	6	2		443					178				168	
Rhode Island.....				35		5							63	
Connecticut.....			1	265	1	42	1		40			2	109	
MIDDLE ATLANTIC														
New York.....	2		2 ¹	1,731	8	281	2		3 162			2	159	23
New Jersey.....		1	2	1,667	1	72			52				150	
Pennsylvania.....	1	1		777	3	73			81			5	102	
EAST NORTH CENTRAL														
Ohio.....	1		2	399	7	61	1		133				228	9
Indiana.....	4		5	610	1	2	1		59				22	14
Illinois.....			2	978	5	91			46				59	2
Michigan.....	6	2		1,436	3	44			133			1	164	
Wisconsin.....			137	765	9	9			58				104	
WEST NORTH CENTRAL														
Minnesota.....	1		19	292		19			13				47	
Iowa.....				271	1	2	4		4				12	5
Missouri.....	1		2	32		8			5		3		27	
North Dakota.....			14	45		45			12					
South Dakota.....				18					2				3	
Nebraska.....		1	14	209		7	2		15			2	1	
Kansas.....	1			95		9			18				32	
SOUTH ATLANTIC														
Delaware.....				4	2				2				7	
Maryland.....			11	95	4	32			10			2	57	
District of Columbia.....			273	86	1	13	1		7			1	1	
Virginia.....			141	176	1	54	1		12			1	111	4
West Virginia.....	2			635	4	22	1		4				47	11
North Carolina.....	4			283	2		2		5			1	65	
South Carolina.....	2		12	86		8							13	7
Georgia.....	1		34	166		12			3			2	40	
Florida.....	1		6	127		10	5		1			2	8	1

EAST SOUTH CENTRAL									
Kentucky	8	262	3	36	2	10	2	38	13
Tennessee	42	278	4	71	1	16	1	46	3
Alabama	62	127	1	45	3	9	1	46	2
Mississippi	24	66	1			5		6	2
WEST SOUTH CENTRAL									
Arkansas	191	76	1	21		3	10	24	5
Louisiana	6	19	3	41	2	2		3	
Oklahoma	71	20		32		5		1	2
Texas	1,088	1,104	8	312	38	31	4	323	22
MOUNTAIN									
Montana	14	68		1		25	1	9	
Idaho	83	111		3	2	3		40	
Wyoming	126	126		1		1		4	
Colorado	15	164		14	1	10	1	43	1
New Mexico	26	26		4	1	5		37	
Arizona	82	71		12		10		21	1
Utah	351	351		16		5		13	
Nevada		2		2			1		
PACIFIC									
Washington	19	191	2	26	2	37	2	80	
Oregon	24	13		23		22		39	
California	5	777	3		28	117	76	215	3
Total	2,492	15,507	80	1,593	102	1,385	1	2,867	137
Median, 1945-49	9	26,551	75		56	1,968	68	1,965	
Year to date, 19 weeks	2,623	176,323	1,782		1,688	32,090	22	908	2,924
Median, 1945-49	5,012	131,466	1,671		811	40,000	118	928	40,341
Seasonal low week ends	(27th)	(30th)	(37th)		(11th)	(32d)	(35th)	(11th)	(39th)
Since seasonal low week	July 9	July 30	Sept. 17		Mar. 18	Aug. 13	Sept. 3	Mar. 18	Oct. 1
Median, 1944-45 to 1948-49	12,578	398,781	2,643		261	48,529	42	398	71,513
						75,650	172	455	69,349

¹ Including cases reported as salmonellosis.

² New York City only.

³ Including cases reported as streptococcal sore throat.

⁴ Excludes 40,200 cases estimated by county health officers to have occurred in Kentucky during the period Jan. 1 to Apr. 8, 1950, and 4,000 cases estimated to have occurred in Jones County, Iowa.

⁵ Deduction: Arkansas, week ended Apr. 20, 1 case.

⁶ *Anthrax*: Pennsylvania, 1 case.

⁷ Alaska: Influenza 25, whooping cough 7.

⁸ Hawaii: Influenza 10, measles 1, poliomyelitis 1.

TERRITORIES AND POSSESSIONS

Hawaii Territory

Plague (rodent).—Under date of May 8, 1950, plague infection was reported proved in a mass inoculation of tissue from 15 rats trapped March 16 and 29, 1950, on the Island of Maui, T. H., in the Paia Gulch, which is within the endemic area of Makawao District.

DEATHS DURING WEEK ENDED MAY 13, 1950

	Week ended May 13, 1950	Corresponding week, 1949
Data for 94 large cities of the United States:		
Total deaths.....	9,212	8,973
Median for 3 prior years.....	9,390	
Total deaths, first 19 weeks of year.....	186,542	184,434
Deaths under 1 year of age.....	587	611
Median for 3 prior years.....	746	
Deaths under 1 year of age, first 19 weeks of year.....	11,876	12,478
Data from industrial insurance companies:		
Policies in force.....	69,811,135	70,402,753
Number of death claims.....	14,536	12,656
Death claims per 1,000 policies in force, annual rate.....	10.9	9.4
Death claims per 1,000 policies, first 19 weeks of year, annual rate.....	10.0	9.7

FOREIGN REPORTS

CANADA

Provinces—Notifiable diseases—Week ended April 29, 1950.—Cases of certain notifiable diseases were reported by the Dominion Bureau of Statistics of Canada as follows:

Disease	New-found-land	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia	Total
Brucellosis.....					5		1	1			7
Chickenpox.....			2	7	143	211	59	10	45	132	609
Diphtheria.....					3		1	1	1		6
Dysentery:											
Amebic.....						3					3
Bacillary.....						2	3	1			6
German measles.....			54		24	1,531		69	163	280	2,121
Influenza.....			1			32	3			11	47
Measles.....				1	557	638	51	69	41	147	1,504
Meningitis, meningococcal.....											
Mumps.....			114		154	576	7	53	128	359	1,391
Poliomyelitis.....										1	1
Scarlet fever.....	1		5	1	95	33	1	6	36	7	185
Tuberculosis (all forms).....	8		2	4	92	35	13	13	2	37	206
Typhoid and paratyphoid fever.....				1	2	1					4
Venereal diseases:											
Gonorrhea.....	9		11	18	70	35	22	16	32	54	267
Syphilis.....	5		7	6	55	12	7	3	7	13	115
Whooping cough.....			33		48	140	10			21	252

CUBA

Habana—Notifiable diseases—4 weeks ended March 25, 1950.—Cases and deaths of certain notifiable diseases were reported in Habana, Cuba, as follows:

Disease	Cases	Deaths	Disease	Cases	Deaths
Chickenpox.....	23	1	Scarlet fever.....	1	-----
Diphtheria.....	21	-----	Tuberculosis.....	9	-----
Malaria.....	2	-----	Typhoid fever.....	11	-----
Measles.....	4	-----			

Provinces—Notifiable diseases—4 weeks ended March 25, 1950.—Cases of certain notifiable diseases were reported in the Provinces of Cuba as follows:

Disease	Pinar del Río	Habana ¹	Matanzas	Santa Clara	Camaguey	Oriente	Total
Cancer.....	3	19	13	20	3	17	75
Chickenpox.....	-----	24	1	63	29	17	134
Diphtheria.....	-----	28	1	1	-----	1	31
Leprosy.....	-----	3	-----	1	-----	2	6
Malaria.....	2	1	1	-----	2	18	24
Measles.....	-----	4	-----	2	35	58	99
Poliomyelitis.....	-----	1	-----	-----	-----	-----	1
Scarlet fever.....	-----	1	-----	-----	-----	-----	1
Tuberculosis.....	4	18	9	22	16	17	86
Typhoid fever.....	4	14	2	13	5	19	57
Whooping cough.....	-----	8	-----	10	-----	1	19

¹ Includes the city of Habana.

INDOCHINA (FRENCH)

Poliomyelitis.—According to information dated May 10, 1950, an outbreak of poliomyelitis has occurred in North Viet Nam (Tonkin), French Indochina. As of May 4, 304 cases had been reported, 254 of which occurred in Hanoi.

JAMAICA

Notifiable diseases—5 weeks ended April 29, 1950.—Cases of certain notifiable diseases were reported in Kingston, Jamaica, and in the island outside of Kingston, as follows:

Disease	Kingston	Other localities	Disease	Kingston	Other localities
Chickenpox.....	19	159	Poliomyelitis.....	1	-----
Diphtheria.....	2	-----	Puerperal sepsis.....	-----	1
Dysentery, unspecified.....	-----	1	Scarlet fever.....	-----	1
Erysipelas.....	-----	1	Tuberculosis (pulmonary).....	57	74
Leprosy.....	-----	4	Typhoid fever.....	6	48
Meningitis, meningococcal.....	1	-----	Typhus fever (murine).....	3	1

REPORTS OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER RECEIVED DURING THE CURRENT WEEK

NOTE.—The following reports include only items of unusual incidence or special interest and the occurrence of these diseases, except yellow fever, in localities which had not recently reported cases. All reports of yellow fever are published currently.

A table showing the accumulated figures for these diseases for the year to date is published in the PUBLIC HEALTH REPORTS for the last Friday in each month.

Cholera

Pakistan.—During the week ended April 22, 1950, 17 cases of cholera, with 7 deaths, were reported in the port of Dacca.

Plague

China.—Reports received recently give the following figures on the reported incidence of plague in China during the year 1949: Fukien Province 376 cases, 207 deaths; Kwangtung Province 93 cases, 54 deaths; Kiangsi Province 25 cases, 11 deaths; Chekiang Province 20 cases, 14 deaths.

Ecuador.—During the period March 1–15, 1950, plague was reported in Ecuador as follows: In Loja Province, at Ciruelos, Catacocha County, one case, at Pindal, Celica County, one case; in El Oro Province, at Capiro, Pinas County, 4 cases.

Union of South Africa.—During the week ended April 29, 1950, three fatal cases of plague were reported at Reitfontein Farm, Thaba 'Nchu District, Orange Free State.

Smallpox

Indonesia—Borneo.—During the week ended April 22, 1950, 71 cases of smallpox with 18 deaths were reported in Pontianak, and 29 cases with 3 deaths were reported during the week ended April 29. During the week ended April 15, 1 case was reported in the port of Bandjermassin.

Pakistan.—Forty-seven cases of smallpox with 35 deaths were reported in Dacca during the week ended April 22, 1950.